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Comprehensive two-dimensional gas chromatography in forensic science: A critical review of recent trends

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ABSTRACT

Comprehensive two-dimensional gas chromatography (GC × GC) has become accepted as one of the most powerful separation techniques in several application areas. In forensic investigations, however, it has not yet been entirely established due to limitations regarding standardized methodology, data interpretation and consistency of results. Nevertheless, GC × GC allows for target analysis, compound class analysis and chemical fingerprinting of samples and is therefore increasingly applied in forensic analytics. In this review, recent and significant advances in GC × GC for application to forensic studies including human scent, arson investigations, security-relevant substances and environmental forensics are discussed. The discussion includes a brief overview of the latest trends and evolutions with regard to the various forensic applications and data evaluation as well as limitations. This leads to the conclusion that the full potential of the comprehensive data sets can only be achieved by implementing standardized analysis and data processing methods.

1. Introduction

Achieving optimized separation for target analytes, compound classes or complete chemical profiles is one of the main challenges in applied chromatography. Compared to one-dimensional gas chromatography (^{1}D GC), comprehensive two-dimensional gas chromatography (GC × GC) provides greater peak capacity, highly structured chromatograms, and in case of cryogenic modulation increased signal intensity. Especially the chromatographic structure allows for chemical fingerprinting, group-type analysis and improved target analysis. Therefore, GC × GC has become one of the most powerful techniques for several applications and has been well established in areas like environmental science, metabolomics, petroleomics and foodomics [1].

Since the advent of GC × GC, first described by Giddings [2] in 1984 and applied by Liu and Phillips [3] in 1991, modification and advances for sample introduction technologies, GC columns, modulation devices, detection systems and data analysis strategies have evolved. Recent improvements are related to reliable chemical identification and the selection of meaningful information [1,4]. In

Abbreviations: μECD, Micro-electron capture detector; ^{1}D, One-dimensional; ^1t_R, Primary retention times; ^{2}D, Two-dimensional; ^2t_R, Secondary retention times; ANOVA, Analysis of variance; CBRN, Chemical, biological, radiological, nuclear; CWAs, Chemical warfare agents; DDTs, Dichlorodiphenyltrichloroethanes; DoE, Design of experiments; EI, Electron ionization; ENCI, Electron capture negative chemical ionization; FFF, Fracturing, flowback and drilling fluids; FID, Flame ionization detection; FRs, Fisher ratios; GC, Gas chromatography; GC × GC, Comprehensive two-dimensional gas chromatography; HCA, Hierarchical cluster analysis; HR, High-resolution; HS-SPME, Headspace solid-phase microextraction; KMD, Kendrick mass defect; kNN, k nearest neighbor classification; LC, Liquid chromatography; MCCPs, Middle-chained chlorinated paraffines; MOECC, Ministry of the Environment and Climate Change; MS, Mass spectrometry; MW, Macondo Well; NAFCs, Naphthenic acids fraction compounds; NPD, Nitrogen phosphorus detection; PBDEs, Polybrominated diphenyl ethers; PCA, Principal component analysis; PCBs, polychlorinated biphenyls; PCDD/Fs, Polychlorinated dibenzo-p-dioxins and dibenzofurans; PCNs, Polychlorinated naphthalenes; POPs, Persistent organic pollutants; qMS, Quadrupole-MS; qTOF, Quadrupole-TOF; RFF, Reverse fill/flush; SCCPs, Short-chained chlorinated paraffines; TAS, Triaromatic steroids; TD, Thermal desorption; TIC, Total ion current; TOF, Time-of-flight; US, United States; VOCs, Volatile organic compounds; VX, O-ethyl S-2-diisopropylaminoethyl methylphosphonothiolate.

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particular, coping with large sample sizes requires robust data processing and statistical methods. Although increased resolving power of co-eluting compounds makes GC × GC promising for trace analysis in crime investigations, it is still an emerging analytical technique in forensic science.

Forensic science is a dynamic field that applies scientific principles and methods to material recovered from the crime scene in order to discover, identify and prosecute criminals [5]. For admission to court, the suitability of a scientific method must be demonstrated. In Europe, the admission of scientific evidence in court depends on the examining judge, who usually relies on accredited experts. Furthermore, parties in European courts have the possibility to ask specific and supplementary questions to the expert, to comment on the expert's report, to requests a second opinion, to requests clarification at the hearing and to ask for an interview of their own private expert [6]. In environmental forensics, the United States (US) Supreme Court set standards for the inclusion of scientific statements, the Daubert criteria, which refer to empirical verifiability, peer-reviewed publications, error rates, use of standards and controls, and general acceptance of the method in the scientific community [7]. So far, these standards have not been verified for GC × GC applications.

To ensure confidence in applicability and data quality, accreditation of a method proves that the laboratories follow appropriate procedures [7]. The first accredited GC × GC method for routine application has been developed by the Canadian Ministry of the Environment and Climate Change (MOECC) Laboratory Services Branch (Toronto, Ontario) utilizing GC × GC coupled to a micro-electron capture detector (μECD) for the analysis of persistent organic pollutants (POPs) in soils, sediment and sludge [8]. Although GC × GC is used in various research groups, there is still a lack of sufficient validated standard methods, based on large well-designed studies, and chemical databases allowing for source apportionment. In general, the transfer of targeted ^{1}D GC to non-targeted GC × GC as a routinely accredited method has been limited by ease of use and robustness. Additional, challenges in forensic investigations e.g. forensic taphonomy, include high analytical costs, lack of reference materials and limitation of replicates [9].

Forensic interpretation and evaluation of evidence is based on data acquired from a large range of sites and sources. Common matrices encountered in a forensic context (environmental specimens, for example) are highly complex in both potential target compounds and also matrix coextractables [1]. To date, the potential of GC × GC has been demonstrated in forensic applications including the study of illicit drugs, CBRN (chemical, biological, radiological, nuclear) agents, explosives, forensic toxicology, arson investigations, forensic taphonomy and environmental forensics [4]. For such investigations, the analysis spans a large variety of sample types containing numerous compound classes (e.g. hydrocarbons, alcohols, aldehydes, aromatics, carboxylic acids, ester, ether, ketones, halogenated compounds, etc.). Most commonly the simultaneous detection of several classes is required. Providing comprehensive insight of the chemical composition, GC × GC is perfectly suited for this type of studies, especially if compared to ^{1}D GC [4].

Depending on the analytical question, different approaches are applied in GC × GC including targeted- and discovery-based analysis, structural classification of analytes as well as chemical fingerprinting [1,4]. Lately, GC × GC fingerprint analysis has mainly been adapted for illicit drug analysis and decomposition profiling, as well as arson and explosives investigations; whereas targeted analysis has been utilized extensively in environmental studies. Evolutions in GC × GC for use in forensics are driven by present challenges such as the complexity of matrices, the diversity of compound classes and the generation of large data sets [1]. In this review, recently published peer-reviewed research articles are discussed to illustrate the changing trends and future directions of GC × GC in forensic science. This study focuses on the application of GC × GC in certain areas of forensic science that were reported frequently and recently, but does not cover the complete spectrum of forensic applications for food authentication/adulteration or data evaluation techniques.

2. Forensic applications

A review focusing on the forensic potential of GC × GC has been published very recently [4]. Since then, the number of forensic studies using GC × GC has risen sharply, the application has even been extended to further areas such as the forensic profiling of human hand odour. Hence, this review covers the latest advances in GC × GC for its use in forensic studies to provide scientists in industry, academia and service laboratories an overview of recent trends, potentials and limitations of GC × GC applications. According to a literature search performed using Web of Science, 57 peer-reviewed research articles were published between 2014 and 2018 applying GC × GC for human scent (Section 2.1), arson investigations (Section 2.2), security-relevant substances (Section 2.3) and environmental forensics (Section 2.4). The studies are discussed with focus on popular sample preparation methods, column sets, statistical analysis as well as results and recent trends. A short paragraph (Section 3) is dedicated to chemometrical approaches, which have been used in forensic studies by GC × GC for the extraction of significant information from the complex data sets. Special attention was paid to exploiting the potential of GC × GC in the various forensic areas.

2.1. Human scent

The profile of volatile organic compounds (VOCs) released by the human body provides valuable information about the characteristic odour of an individual. This unique volatile profile can be used to monitor human presence [4]. In forensic profiling and taphonomy the volatile fingerprint can be tracked by specially trained canines in the investigation of crime scenes or in rescue missions [10–12]. For a deeper understanding of human odour detection by canines, detailed chemical insight of the molecular composition of such profiles is needed. GC × GC-TOF-MS has been successfully demonstrated for the characterization of high complex odour profiles in human profiling and decomposition studies.

2.1.1. Forensic profiling

An optimized GC × GC method for the forensic profiling of human hand odour has recently been presented by Cuzuel et al. [11]. The group proposed a statistical approach for assessing the orthogonality of GC × GC, targeting 80 potential VOCs. Based on nine defined criteria, e.g. separation efficiency and run time optimization, 27 different GC × GC setups were compared amongst each other. The results suggested that a normal phase column set (nonpolar ^{1}D by polar ^{2}D) yield best results for the analysis of the used VOC mixture. The main limitation of the study was the lack of application to hand odour samples. In contrast, female skin scent was investigated by Doležal et al. [12] using a non-targeted approach for the qualitative analysis of less volatile molecules. GC × GC allowed for an improved identification of potential human scent markers. However, since the separation space was not sufficiently used, qualitative improvement relative to ^{1}D GC was not so obvious. Furthermore, the benefits of GC × GC in this study were demonstrated by group type analysis of human skin scent, with special attention on fatty acid esters.

2.1.2. Forensic taphonomy

The unique odour created by decomposing remains, the "smell of death", is still little understood due to the complex and dynamic decomposition process and the lack of consensus in results [5,10,13]. Therefore, this subject has been extensively studied by GC × GC coupled to time-of-flight mass spectrometry (TOF-MS) applied to the headspace of textiles associated with decaying remains [13], the headspace of deceased bodies (human remains [14] and pig carcasses [14–19]), soil gas (from human remains [20] and pig carcasses [9,16,17,21–23] decomposition), adipocere samples [20], human internal cavity gases [24,25] and human blood [26], which yielded detailed insight in post-mortem changes of VOC profiles. With regards to field studies and analysis, thermal desorption (TD) and the combination of a midpolarity cyanopropyle phase (Rxi-624Sil MS, ^{1}D) and a polar polyethylene glycol phase (Stabilwax, ^{2}D) has been demonstrated to be the most effective sampling method and column setup for the comprehensive investigation of cadaveric VOCs [10]. The high peak capacity of GC × GC separation combined with high resolution (HR) mass spectral data provides an added value in improving compound assignment [9,20,24,25].

Simplifying the interpretation of GC × GC data, the research groups of Forbes and Focant reported the extraction of the most informative variables applying a combination of statistical approaches such as analysis of variance (ANOVA) [20,25,26], Fisher ratios (FRs) [9,13–15,19,20,24,26], Hierarchical cluster analysis (HCA) [20,24,26] and principal component analysis (PCA) [9,13–15,18,19,21,22,26]. Commercially available tools, such as "Statistical Compare" (ChromaTOF) and "Image Investigator" (GC Image) as well as advanced statistical analysis software such as "The Unscrambler® X" (CAMO Software) have been implemented. Hence, improved data visualization of distinct VOC profiles in different classes was demonstrated on the example of three days of active decay by plotting the distribution of the FR values over the chromatographic retention plane demonstrating the significance of additional separation in GC × GC (Fig. 1) [19].

The effect of aging on blood volatiles was investigated by Dubois et al. [26] by TD-GC × GC with a reverse fill/flush (RFF) flow modulator coupled to a BenchTOF-Select TOF-MS (Markes International Ltd.). Highly volatile compounds down to C_4 were effectively modulated even though the modulator induced a decrease in sensitivity. A three-step identification procedure based on 70 eV mass spectra, retention indices and 14 eV mass spectra led to increased certainty of identified substances belonging to compound classes such as alkanes, aromatics and ketones as well as mono-chloroalkanes.

A non-destructive post-mortem examination of the volatile profile of gas reservoirs inside the human body was reported by Stefanuto et al. [24]. Applying headspace solid-phase microextraction (HS-SPME) combined with GC × GC-HRTOF-MS inter- and intra-body variations were investigated. The volatile pattern of various cavities from four different deceased individuals were compared in this proof-of-concept study. The main advantage of coupling GC × GC with HRTOF-MS was improved compound identification. Further results included a trend of tissue-specific VOCs and higher inter-body variances compared to intra-body variances. Following these findings, Perrault et al. [25] evaluated method parameters with regard to selectivity, sensitivity and data quality. The optimized methodology was applied to the analysis of VOCs in several internal gas reservoirs from five individuals. A total of 29 potential VOCs marker substances were reported.

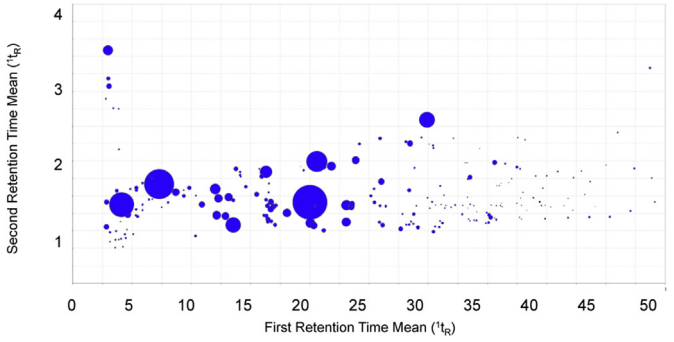

Fig. 1. Visualization of potential VOCs for the distinction of three days of active decay. By applying Fisher ratios on the data set to create two-dimensional Fisher ratio plots, 221 peaks of interest were found to have the maximum potential for class differentiation. Reprinted with permission from Ref. [19].

Due to legal and ethical restrictions on studying human remains, most decomposition studies involve pig carcasses. Similar trends in early decomposition stages to human odour analogues have been demonstrated [14]. Nevertheless, the restricted number of available replicates complicates statistical analysis. This is commonly recognized as a limitation of cadaveric decomposition profiling [22]. For the investigation of cadaveric profile (human and porcine), GC × GC has been applied to the analysis of alcohols, aldehydes, ketones, aromatics, carboxylic acids, ester, ether, hydrocarbons, halogenated, N-containing and S-containing VOCs. These compound classes were investigated for the distinction of post-mortem phases [14,15], the ability of textiles to retain a detectable odour [13], the impact of probing [16], decomposition VOCs in soil [20–22], the effect of entrapment conditions [17] and the impact of seasonal variations to the VOC profile [18,23]. Recently, the potential of GC × GC-HRTOF-MS for application to forensic investigations at a death scene was demonstrated by Dubois et al. [20] for the first time. Characteristic VOC patterns of adipocere dominated by volatile carboxylic acids and acid esters may provide evidence of a carcass-specific decomposition.

2.2. Arson investigations

In most cases that involve arson, petroleum-based liquids are used as accelerants. These accelerants are inherently complex, volatile mixtures that could originate from a large variety of sources. Nizio et al. [27] reported an optimized GC × GC method for the analysis of ignitable liquids. The combination of sharp reinjection pulses, long 2nd dimension columns, identical inner diameter as well as optimum flow and heating rates yielded in a method with a peak capacity of only 17% below the theoretical maximum in peak capacity. High peak capacities result in higher dimensional datasets. Therefore, Lopatka et al. [28] applied a data reduction strategy based on local ion signatures and a likelihood framework to data from designed burn experiments. Exhibiting false positive rates <1% and a feature selection protocol, this method allows for intuitive selection and discovery of chemical information. A study by Sampat et al. [29] was set out to determine brand to brand differences and temporal variations within white spirit samples based on GC × GC profiles. The results showed that brand-to-brand and production variances are quite limited, whereas the temporal variations are high.

2.3. Security-relevant substances

Monitoring illicit substances such as illegal drugs, explosives and chemical warfare agents (CWAs) is of particular importance for public security in strategic locations, but also for the identification of their origin/history which can be used as evidence in court [4]. The low detection limits demanded usually result in targeted approaches [30], which would neglect derivatives, transformation products or relevant contaminants. Due to its high separation

capacity, GC × GC-MS allows for both targeted and untargeted analysis and is therefore of particular forensic interest for the identification, characterization and classification of material containing illegal substances [4]. Recently, GC × GC-MS has been applied to the study of nerve agents [31], explosives [32,33] and illicit drugs such as cannabis [30,34], heroin [35], and steroids [36,37]. To efficiently separate security-relevant trace components from matrix interferences in GC × GC, the trend is towards a normal phase column set.

2.3.1. Chemical warfare agents

Gravett et al. [31] studied the effect of various decontamination treatments on the persistent nerve agent O-ethyl S-2-diisopropylaminoethyl methylphosphonothiolate (VX) in a model soil. LC-HR-MS, GC-MS-dualFPD and GC × GC-TOF-MS were compared with respect to the detectability of 30 marker compounds. Utilizing GC × GC, this study visually demonstrates that VX and the majority of its impurities and stabilizing chemicals remained detectable after accelerant-enhanced fires.

2.3.2. Explosives

Highly accurate sample classification based on GC × GC-TOFMS data was reported by Tsai et al. [32]. The application of a statistical toolset allowed for the differentiation of production batches of plastic explosives. Aligned peak lists were investigated using *k* nearest neighbor classification (kNN) and PCA after different normalization procedures. The data treatment was thereby comprised of normalization (sample mass or total peak area), conversion to normalized profile data and standardization of profile data, as well as appropriate statistics such as PCA-based kNN. The lowest misclassification was achieved using the total ion current (TIC) area for normalization followed by mean centering and scaling. The study demonstrated that a highly accurate classification of samples can be observed using GC × GC in combination with simple and effective data treatment. For a decreased degradation of explosives during analysis, Stefanuto et al. [33] applied SPME in combination with fast reversed phase (polar ^{1}D by nonpolar ^{2}D) GC × GC-TOFMS. Applying FRs and PCA, SPME-GC × GC-TOFMS enabled improved characterization of explosives compared to liquid injection. Environmental impurities, which were only resolved by high separation capacity, provided important information about the sample history.

2.3.3. Illicit drugs

Applying a design of experiments (DoE) optimized SPME-GC × GC-MS method, Marchini et al. [30] differentiated the volatile chemical profiles of cannabis derived products. Compared to ^{1}D-profiles, compound identification was greatly improved. Prominent compound classes, responsible for the differences between the cannabis herb and hashish samples, contain mono- and sesquiterpenes. For further improvement of peak resolution in GC × GC-qMS data of *cannabis sativa* extracts, Omar et al. [34] applied multivariate curve resolution combined with an alternating least squares algorithm. This data treatment was able to partially compensate for detector induced shortcomings e.g. acquisition frequency. Therefore, the differentiation between buds, leaves and different plants could be shown even by the application of low resolution detection.

Chemical profiling of illicit drugs based on impurities was conducted by Zimmermann and co-workers [35] for samples taken from different steps in the heroin manufacturing process. Impurity profiles of different production stages were studied applying GC × GC-TOFMS. To visualize qualitative information, ^{2}D apex bubble plots were generated for the differentiation of compound classes (colour coded), shown in (Fig. 2). Using this approach, potential markers for forensic investigation in heroin impurity could be detected.

To improve the analytical performance of GC × GC in anabolic agent investigations, thermodynamic modelling for retention time predictions was applied by Silva et al. [36]. The observed results showed a relative error in predicted secondary retention times ($^{2}t_R$) of an order of magnitude larger than for predicted primary retention times ($^{1}t_R$), presumed due to varying film thicknesses in ^{2}D column segments. However, predicted $^{1}t_R$ and $^{2}t_R$ showed good agreement with experimental results, and therefore could be used for the establishment of a thermodynamic library and a quantitative structure-property relationship model. Monitoring of hormone active steroidal compounds has become of increasing importance in clinical laboratories, but also in environmental forensics due to its accumulation into the environment by reusing sewage sludge of waste water treatment plants. In this context, Kopperi et al. [37] showed the benefits of non-targeted GC × GC in combination with chemometric data evaluation for studying the fate of steroidal compounds during waste water treatment. The usage of statistical tools enabled the screening for variances between sample sites without the requirement of time-consuming identification and quantification of individual compounds.

2.4. Environmental forensics

Environmental forensics is primarily directed towards detecting entities responsible for releasing illegal and/or harmful components into the environment. Hence, environmental forensics addresses the composition, origin, persistence and fate of these contaminants.

2.4.1. Persistent organic pollutants

The analysis of persistent organic pollutants (POPs) gives important information regarding the source, age or quantity of contaminants released into the environment. Benefiting from higher peak capacity, GC × GC is commonly applied to separate target POP groups from complex matrices such as tissue, dust, soil, water or bio-fluids. In addition, it is used for the investigation of newly discovered POPs. Mainly normal phase column combinations dominate the reviewed applications. Regarding MS, detection has trended towards HR-MS. Since the ban on the use of short- and middle-chained chlorinated paraffins (SCCPs and MCCPs) (2002 in EU) and their addition to appendix A of the Stockholm Convention (in 2017) these substance classes have received increased scientific attention.

In 2014 Xia et al. [38] presented possibly the first application of GC × GC for the analysis of SCCP. Analysing SCCPs and MCCPs in breast milk in rural regions in China, Xia et al. [39] based the assessment of health risks by SCCPs and MCCPs to infants on a similar group-type based quantification. Taking advantage of the structured nature of GC × GC chromatograms, Muscalu et al. [40] achieved good recovery rates for the detection of SCCP as well as MCCP in sediment samples utilizing a group-type quantification approach. Hashimoto et al. [41] utilized negative chemical ionization and neutral loss scanning HRTOF-MS for discovery based screening of chlorinated and brominated organohalogens. With this study, universally applicable software was introduced to enable the selectively extraction of chlorinated and brominated signatures out of GC × GC-HRMS and GC × GC-MS/MS data files.

Nabi et al. [42] presented a model for the environmental partitioning properties of non-polar POPs such as polychlorinated biphenyls (PCBs), based on GC × GC retention time information (Fig. 3). Predictions regarding long-range transport, arctic contamination potential, aquatic bioaccumulation potential and terrestrial biomagnification potential could be made from the

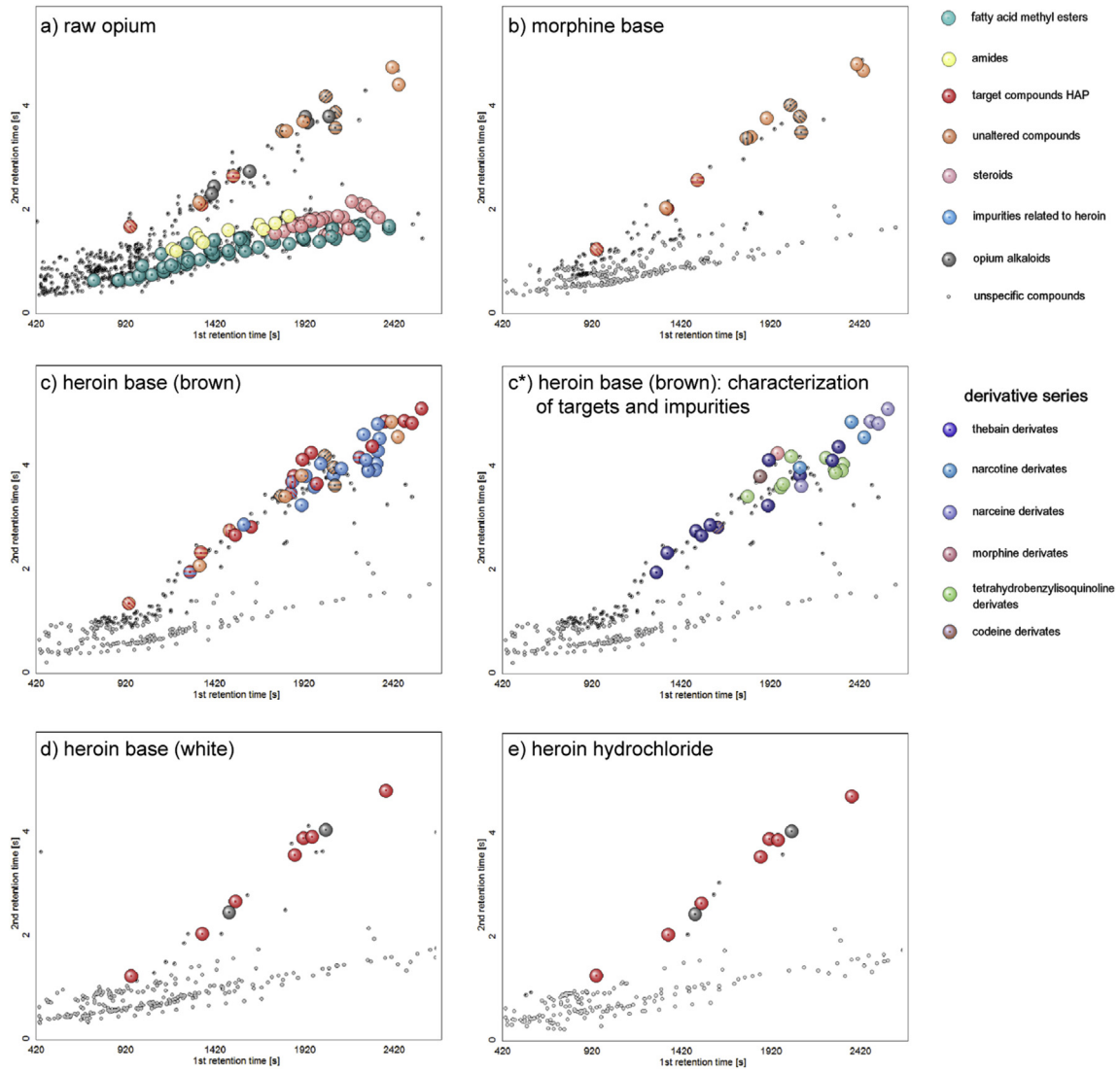

Fig. 2. Visualization of compound class differentiation in GC × GC using apex bubble plots on the example of acidic extracts from different heroin manufacturing steps. a) Raw opium, b) morphine base, c) heroin base (brown), d) heroin base (white), e) heroin hydrochloride. Adapted with permission from Ref. [35].

compound's location in the ^{2}D separation space. The fate of selected pesticides and PCBs in meat following pan cooking procedures was reported by Planche et al. [43,44] in 2015 and 2017. Initial chemometric data processing and GC × GC capability for detailed chemical fingerprinting allowed the discrimination between different meat preparation conditions according to their PCB and Polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs) signature. In 2016 Rimayi et al. [45] screened river sediment samples for bioactivity induced by dioxin like substances. Utilizing GC × GC-μECD, the authors compared theoretical toxicity to the results obtained from their bioassay screening. Their main finding was that the theoretical toxicity value is 4–9 times lower than the screening results, since the assay reacts to dioxins, as well as dioxin-like substances.

Organic solid-water partition coefficients for selected non-polar halogenated micro pollutants in wastewater treatment plants were determined by Dimitriou-Christidis et al. [46]. Additionally, the quantification of 59 targeted compounds by GC × GC led to the detection of less-studied target analytes with bio accumulative potential. Samanipour et al. [47] compared the sensitivity of GC × GC coupled to an electron capture negative chemical ionization (ENCI) TOF-MS and μECD with GC × GC coupled to electron ionization (EI) TOF-MS by quantifying two flame retardants (1,3,5-tribromobenzene and 4-bromobiphenyl) in deep water columns and sediments of Lake Geneva. The findings stated that the sensitivity of ENCI and μECD is elevated compared to common GC × GC-EI-TOF-MS. Nevertheless, it should also be noted that the influence of different modulation devices used towards sensitivity was not considered. Due to the high variety of congeners for POPs it is difficult to obtain commercial standards for quantification and verification. Organtini et al. [48] utilized group type separation by GC × GC-TOF-MS for the assessment of poly halogenated dioxin and furan congeners in commercial and residential fire debris simulations. The study provided a broad list of polyhalogenated compounds based on their occurrence and combustion feedstock.

Instead of separating target compounds from complicated matrices, discovery based analysis focuses on the detection of previously unmonitored substances. Millow et al. [49] described a discovery based approach for the analysis of halogenated organic compounds, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethanes

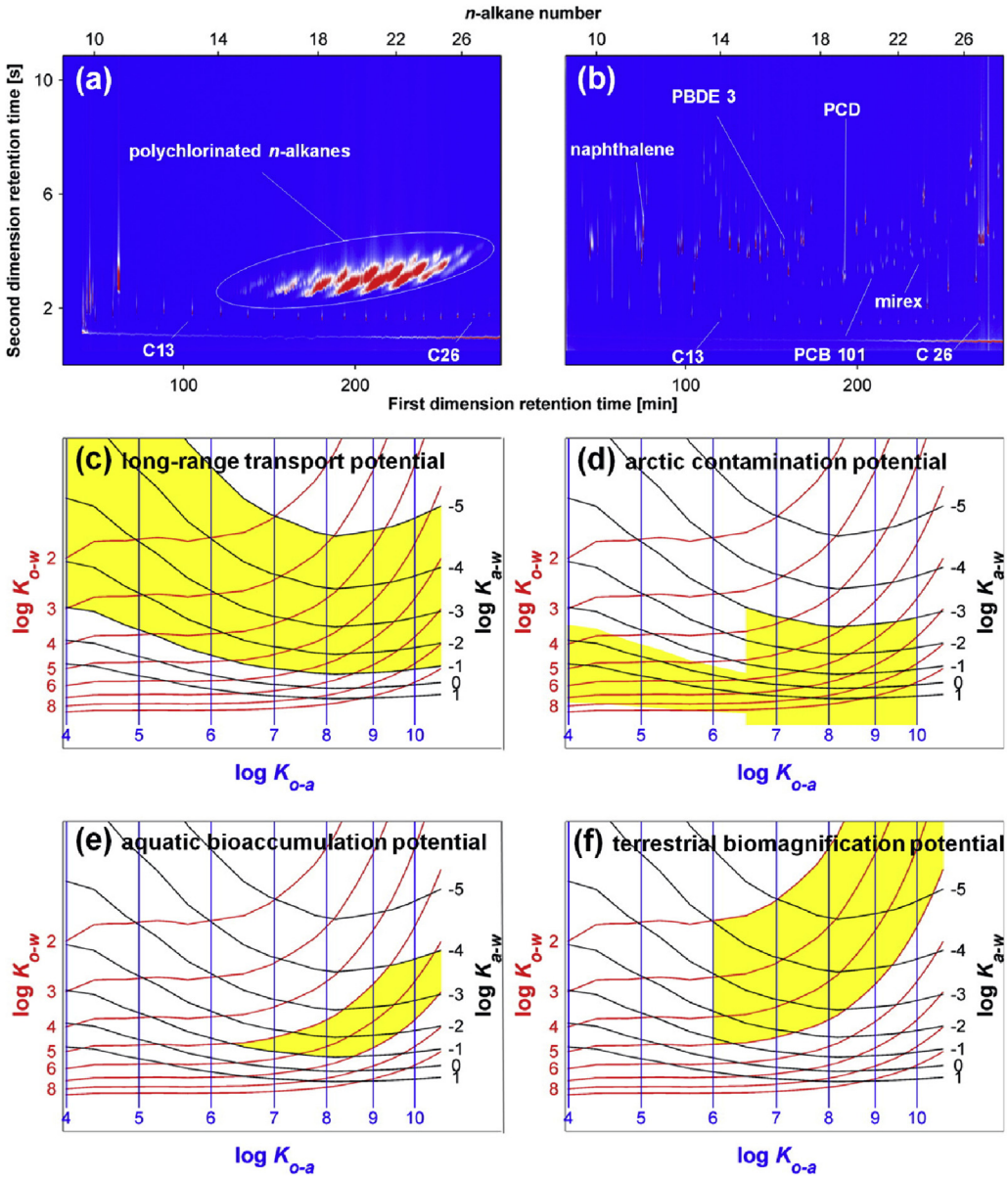

Fig. 3. Mapping environmental behaviours of nonpolar contaminants onto a GC × GC chromatogram of (a) a short-chain polychlorinated alkanes technical mixture and (b) a mixture of injected standards. Lower panels (c–f) show maps of log Ka–w (black contours), log Ko–a (blue contours), and log Ko–w (red contours) overlaid onto the GC × GC retention time space. Shaded yellow regions would contain analytes having (c) long-range transport potential, (d) arctic contamination potential, (e) aquatic bioaccumulation potential, and (f) terrestrial biomagnification potential. Reprinted with permission from Ref. [42], https://pubs.acs.org/doi/abs/10.1021%2Fes501674p. Further permissions related to the material excerpted should be directed to the ACS.

(DDTs) etc., in seabird eggs. Despite small sample size, 27 previously unmonitored halogenated compounds were reported as potential marker substances for bioaccumulation of halogenated organic compounds in seabird sentinels. In a study by Xia et al. [50], the authors compared the application of GC × GC-HRTOF-MS for the quantitative analysis of PCBs and polychlorinated naphthalenes (PCNs) in thornback samples with established ^{1}D methods. The results clearly demonstrated the excellent performance towards lower detection limits for targeted compounds applying GC × GC-HRTOF-MS. Despite being addressed rather incidentally, this study showed that discovery and targeted analysis can and should be performed simultaneously. Combined with HR-MS the evaluation of GC × GC data is quite time intense. Therefore, Ubukata et al. [51] applied non-traditional Kendrick mass defect (KMD) plot based on an averaged mass spectra over the total separation space. The reported approach addresses the identification of unknown organohalogens in complex matrices.

2.4.2. Deepwater horizon

Biomarkers from petroleum sources are often used to identify crude oil spills and gain insight into weathering or persistence of oils. On April 20, 2010, the Deepwater Horizon oil platform exploded, releasing 6.8 ± 1.7 × 10^{8} kg petroleum into the Gulf of Mexico. As much as 10% of the released oil ended up on beaches, thus presenting the need for a fingerprinting methodology such as GC × GC to distinguish Deepwater Horizon hydrocarbons from those associated with accidental releases or natural oil seeps.

In this context, Gros et al. [52,53] applied GC × GC for the determination of hydrocarbon partitioning and mass loss calculations [54]. These models allowed the prediction and verification of

the hydrocarbon composition in oil slick, an estimation for the gas-liquid-water composition of the emitted petroleum mixture during Deepwater Horizon disaster and an assessment of the change in the organic fingerprint. Aeppli et al. [55] investigated the fate of commonly monitored biomarkers including hopanoids, steranes, and triaromatic steroids (TAS) that are used for source and fate determinations of petroleum hydrocarbons. Utilizing GC × GC-TOF-MS and GC × GC coupled to flame ionization detection (FID) for the qualitative and quantitative analysis, the study showed that the common monitored biomarkers are not as stable as generally considered, which can be seen in Fig. 4 on the example of Macondo Well (MW) oil and an oil-soaked sand patty. Such degradation behaviour of commonly monitored biomarkers pose analytical challenges. Damavandi et al. [56] proposed a fast data evaluation strategy based on peak topology maps, enabling the comparison of regions of interest and allowing the inclusion and identification of less-known non-target biomarkers in GC × GC profiles.

2.4.3. Unconventional gas development

The analysis of fracturing, flowback and drilling fluids (FFF) by GC × GC allows for the resolution of various hydrocarbon classes, which are not separable by ^{1}D GC. Llewellyn et al. [57], investigated foaming groundwater samples in the vicinity of five unconventional gas pads. Due to lower detection limits, GC × GC revealed the presence of known hydraulic fracturing additives (2-butoxyethanol, for example) as well as similarities in the hydrocarbon profile between groundwater and reference samples. Stevenson et al. [58] presented an optimized methodology for the detection of alkyl phosphates in nitrogen rich crude oils from hydraulic fracturing processes, which are used as additives in some hydraulic fracturing processes. The study showed that good separation and recovery rates (>80%) for these compounds could be achieved by GC × GC coupled to nitrogen phosphorus detection (NPD) and reversed phase column combination. The complete organic profile of FFF was performed by Dorman and co-workers [59]. Based on group type screening techniques for hydrocarbon profiles, the study claims that the hydrocarbon composition in flowback fluids is more reflective of hydrocarbon interactions with the organic-rich shale. Strong et al. [60] investigated biodegradation and composition waters from oil and shale in the Marcellus and Bakken regions. GC × GC was used for organic group type profiling of the samples, before and after biodegradation. The results can be used as first suggestions towards bioremediation of waters from hydraulic fracturing processes.

2.4.4. Naphthenic acids fraction compounds

Defined as the acid extractable fraction of oil sands and/or petroleum process waters, naphthenic acids fraction compounds (NAFCs) enter the environment mainly through effluent discharge, but also through groundwater mixing and erosion of riverbank oil deposits [61]. Damasceno et al. [62] showed that based on the number of cyclic moieties for NAFCs, GC × GC proved to be advantageous compared to classical ^{1}D techniques for the analysis of NAFCs. Regarding bicyclic compounds as the most acutely toxic compounds in NAFCs, Wilde et al. [63] set out for in depth identification of these compounds. GC × GC was mainly utilized to separate bicyclic compounds from the matrix. In combination with pre-separation [64] and reduction procedures [65] including esterification, reduction, tosylation and reduction, the number of identified compounds was expanded. Furthermore, a pre-separation approach was utilized by Robson et al. [66]. Here, GC × GC was mainly used to obtain better quality mass spectra and to verify the pre-separation process. Taking advantage of the proton accepting behaviour of NAFCs under atmospheric pressure ionization, Bowman et al. [67] reported a method utilizing GC × GC-HRqTOF-MS for the assignment of sum formulas.

3. Chemometrical approaches applied in forensic studies utilizing GC × GC

Admissibility of expert evidence in court is based on reliability, robustness and significance of the analytical data. Therefore, chemometrical tools are required to provide validity as well as statistical certainty of the applied technique. According to Sampat et al.

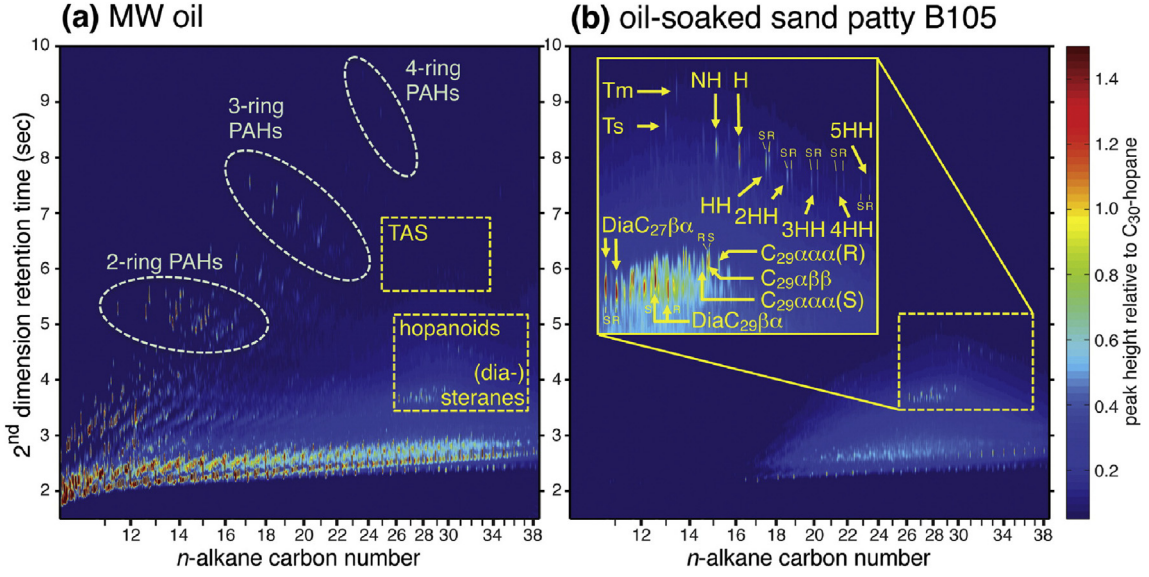

Fig. 4. GC × GC-FID chromatograms of (a) MW oil and (b) sand patty B105 collected in August 2012 in Gulf Shores, AL. Highlighted are two biomarker regions including hopanoids, (dia)steranes and TAS as well as PAH elution regions. Several compound classes present in MW oil have been removed, whereas the hopanoid and (dia)sterane region remained largely unaffected. Reprinted with permission from C. Aeppli, R.K. Nelson, J.R. Radović, C.A. Carmichael, D.L. Valentine, C.M. Reddy, Recalcitrance and degradation of petroleum biomarkers upon abiotic and biotic natural weathering of Deepwater Horizon oil, Environ. Sci. Technol. 48 (2014) 6726–6734. https://doi.org/10.1021/es500825q. Copyright 2018 American Chemical Society.

[4], this includes (a) techniques investigating interferences or impossible interferences of uniqueness and (b) techniques focusing on the comparison of likelihood ratios.

Techniques focused on interference investigations typically include hypothesis testing, classification and prediction techniques. These techniques guide the forensic scientist to evaluate towards optimal sampling strategies or the identification of most likely sources of contamination, ensuring the validity of the data. The second set of techniques, focuses on likelihood approaches to evaluate the evidential strength of the multidimensional results. To obtain likelihood ratios, the chemometrical statistic should follow the Bayesian framework for evaluating evidence. Typically, such techniques strive to obtain reduced sets of features allowing for further multivariate statistical analysis. A combination of chemometrical tools such as PCA with Fisher Criterion or ANOVA allow for comparison between different samples based on significant feature subsets. Compared to ^{1}D GC, this is particularly useful since the information density yielded by GC × GC investigation is typically high and very complex.

Both techniques can be applied in targeted (focused on specific compounds or compound sets) and untargeted (using complete datasets as input) approaches. However, statistical tools used for data evaluation in GC × GC require a high level of expertise and are therefore not yet applicable in routine analysis.

4. Conclusion

Since its introduction, GC × GC has been widely accepted in separation science due to its enhanced peak capacity and sensitivity. Therefore, GC × GC is particularly promising in the field of forensic sciences. In this review, the evolution of GC × GC in forensic studies of human scent, arson investigations, security-relevant substances and environmental forensics has been discussed.

In general, there is a trend towards the usage of the comprehensive GC × GC information for evidence types associated with complex chemical composition. Increased interest is thereby paid to chemical profiling, fingerprinting, group-type characterization and classification. This is true as well for applications, in environmental forensics, aiming at the analysis of petroleum related compounds. For the analysis of persistent organic pollutants, however, GC × GC prevails as a technique for the separation of target compounds and/or compound classes from complex matrices.

Predominantly, normal phase column combinations are used, except in forensic taphonomy. For the analysis of decomposition VOCs, mid-polar: wax column sets have been preferably utilized. Amongst the reviewed research articles, most of the studies applied cryogenic modulation (62% quad-jet cryogenic modulation and 27% loop type modulation). Only a small subset used consumable free modulation devices such as flow modulators (7%) and other types (4%). Almost in three quarters of the studies (71%), GC × GC was coupled to MS detection utilizing EI for chemical identification, whereas only 9% applied FID mainly for quantification purposes. Combinations of MS and FID were reported in 5% of the applications. Regarding the analysis of POPs in environmental samples, μECD, ENCI and their combination proved to be somewhat popular (each 5%).

In particular, in forensic studies of human scent (2.1), security-relevant substances (2.3) and arson investigations (2.2), the detailed chemical information achieved by GC × GC-MS analysis was used for a complete comparison of profiles, taking into account the causality between several samples. Such approaches generally lead to an increased demand of sophisticated GC × GC data analysis techniques. Therefore, an upward trend of reports addressing chemometric approaches for the extraction of significant data was observed. This realization is indeed not new and not only limited to forensics. The reported techniques are still highly experimental, however, and far from being standard. Therefore, specially trained personnel are needed, which is why the techniques are still limited for routine use.

As stated above, environmental forensic studies (2.4) mainly applied GC × GC for the separation of target compounds or compound classes, only few approaches took advantage of the comprehensive information yielded. It is also noteworthy, that with few exceptions [39,42,45,60], the consequential next step of source apportionment or cause/effect relationship has not yet been made. This is most likely due to the fact that GC × GC is not fully established as a relatively new technique in the individual analytical disciplines. This in turn is a logical consequence of the lack of standardized data analysis techniques. For a complete acceptance and utilization of GC × GC, previous considerations for data interpretation need to be revised and updated.

From the studies presented here, the analytical potential of GC × GC for forensic applications becomes clear. However, to establish GC × GC as a routine tool for forensic applications, there is a need of larger studies proving the stability and reproducibility of GC × GC results. Furthermore, robust and standardized analytical methods and data evaluation procedures for targeted- and discovery-based analysis, structural classification of analytes as well as chemical fingerprinting need to be established. In this case, the authors are convinced that GC × GC will be increasingly used for routine forensic investigations, but still being far from its recognition as standard providing scientific evidence in court.

Notes

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